These results are supplied for informational purposes only. *Prescribing decisions should be made based on the approved package insert in the country of prescription*			
Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00545337
		Study Code:	HMR1964A_3505
Generic drug name:	insulin glulisine	**Date:**	26 October 2007

Title of the study:	Multicenter, open, non-randomised phase III clinical study of efficacy and safety of insulin glulisine (HMR1964) injected subcutaneously in patients with type 1 diabetes mellitus using also insulin glargine during 26 weeks of therapy (HMR1964A_3505)
Investigator(s):	-Endocrinology Scientific Center of Russian Academy of Medical Sciences. Dm. Ulianova str., 11, Moscow, 117036, Prof Shestakova M. -Moscow Medical Academy named after I.M. Sechenov, Endocrinology Clinic. Pogodinskaya str., 1/1, Moscow, 19881, Prof Melnichenko G. -I.P.Pavlov St-Peterburg State Medical University, Municipal Clinical Hospital №2. Uchebniy per., 5, St-Peterburg, 194354, Dr Zalevskaya A. -St-Petersburg Medical Academy for Advanced Medical Studies, St. Elizabeth Municipal Clinical Hospital. Vavilovykh str., 14., St- Peterburg, 195257, Prof Vorokhobina -Moscow State Medico-Stomatologic University, City Clinical Hospital #6 Durova str.,26/3, Moscow, 109090, Prof Mkrtoymyan -Russian Academy for Advanced Medical Education. Chasovaya 20 str, Moscow, 125315, Prof Ametov A. -Moscow Medical Academy named after I.M. Sechenov, Moscow City Hospital #67. Salyam Adily str, 2, Moscow, 123448, Prof Balabolkin M.
Study center(s):	7 in Russia

Publications (reference):		
Study period: Date first patient enrolled: 22/Sep/2004 Date last patient completed: 18/Feb/2005		**Phase of development:** III
Objectives:	To provide local data on efficacy and safety of insulin glulisine in patients with T1DM receiving insulin glargine as basal insulin therapy	
Methodology:	The study consisted of 2 periods: − **introduction period** of at least 4 weeks, when insulin glargine was introduced as a basal insulin and titrated in accordance with algorithm based on mean FBG; **− treatment period of 26 weeks** – when previous prandial insulin was switched to insulin glulisine	
Number of patients: **Evaluated:**	Planned: 140 Efficacy : 139	Safety: 142
Diagnosis and criteria for inclusion:	- Type 1 diabetes mellitus - ≥ 18 years old - HbA1c 6.5-11.0% - informed consent form to participate in the study - BMI <35 kg/m2	
Investigational product: Dose: Administration:	Insulin Glulisine Insulin glulisine was to be titrated to achieve the titration goals of 2-hour postprandial BG value 6.7-8.9 mmol/l subcutaneous	
Duration of treatment: 26 weeks		**Duration of observation:** 4 weeks

Reference therapy: Dose: Administration:	Insulin glargine Insulin glargine was to be titrated based on FBG level. The titration goal was 5.0- 6.0 mmol/l subcutaneous
Criteria for evaluation:	
Efficacy:	**Primary:** Change of HbA1c from baseline to endpoint. **Secondary:** Change in HbA1c from baseline (week 1) to weeks 12 and 26, blood glucose parameters, hypoglycaemic episodes and dosage of the mealtime and basal insulins
Safety:	Adverse events, clinical chemistry, haematology
Statistical methods:	**Efficacy:** Primary: Change of HbA1c from the baseline to the endpoint in the PP population=139. Secondary: Analyses of all secondary variables in the PP population. **Safety:** Treatment-emergent adverse events

Summary:	PP population=139 pts, ITT population= 142 pts Insulin glulisine, injected subcutaneously in patients with Type 1 diabetes mellitus using also insulin glargine has a high clinical efficacy in terms of decrease of HbA1c (8.18 to 7.46%, p<0.00001). In average, fasting glycemic levels decreased from 7.1 to 6.3 mmol/l (p<0.0005) (PP, N=139) from baseline (week1) to the end of treatment (week 26). Post-prandial glycemia decreased from baseline (week1) to the end of treatment (week 26): mean of 2-hour glycemia after dinner decreased from 8.1 to 7.5 mmol/l, after breakfast 7.9 to 7.2 mmol/l, after lunch 8.1 to 7.6 mmol/l. (PP, N=139) During the study period the rate of all types of hypoglycemia decreased. None patients refused from the participation of the study. All completed patients continued the study medication in the Extension study.

Efficacy results:

Table 1. Change of HbA1c (%) during the study treatment.

N= 139	Mean	Std.Dev	95%CI		Max	Median	Min
Week-4 (introduction of Ins.glargine)	8.52	1.37	8.29	8.75	11	8.3	6.5
Week1 (baseline)	8.18	1.44	7.94	8.42	12.7	8	5.1
Week 12	7.7	1.26	7.49	7.92	10.9	7.6	4.8
Week 26	7.46	1.16	7.27	7.66	10.9	7.4	5.0
Change from baseline to week 26 (end)	-1.1	1.04	-1.23	-0.88	1.7	-0.9	-3.7

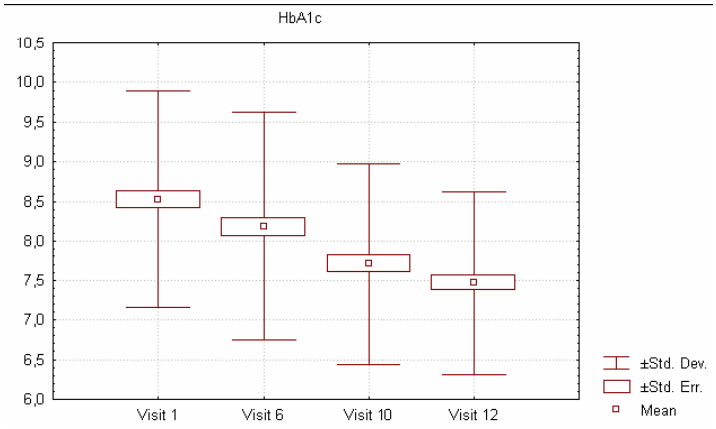


Fig 1: Change of HbA1c (%) during the study treatment

Efficacy results:

Table 2: Allocation of patients (N, %) in accordance with the HbA1c level

HbA1c N=139	Introduction of glargine (Week -4)	baseline Week 1	Week 12	Week 26
≤ 7.0 %	26 (18.7%)	31 (22.3%)	43 (30.9%)	49 (35.3%) p=0.0193
> 7.0	113 (81.3%)	108 (77.7%)	96 (69.1%)	90 (64.7%)

Table 3: Change of the mean of post-prandial glycemia during the study treatment

mmol/l	Baseline	Insulin glulisine treatment					
PPG	Week1	Week 2	Week 4	Week 8	Week 12	Week 18	Week 26
2-hour after breakfast	**7.9 ±2.3**	7.4± 1.9 p=0.0008	7.6±1.9	7.6 ±1.9	7.5 ±2.1	7.4± 1.9	**7.2± 1.5** p=0.00002
2-hour after lunch	**8.1 ±2.0**	7.8± 2.0 p=0.04	7.7 ±2.1	7.8± 1.9	7.9± 2.2	7.7± 1.8	**7.6± 1.8** p=0.02
2-hour after dinner	**8.1 ±2.1**	7.6 ±2.0 p=0.01	7.7 ± 1.8	7.8± 1.9	7.3 ±2.5	7.5± 1.7	**7.5± 1.7** p=0.0006

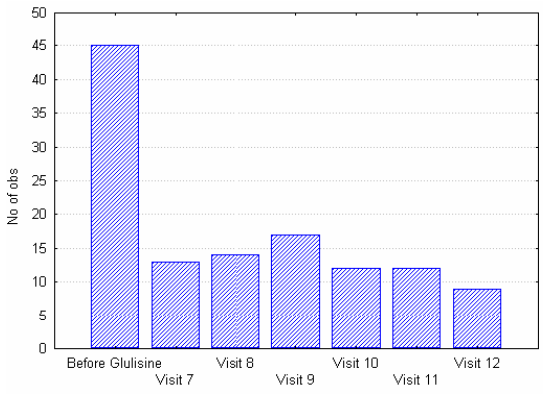
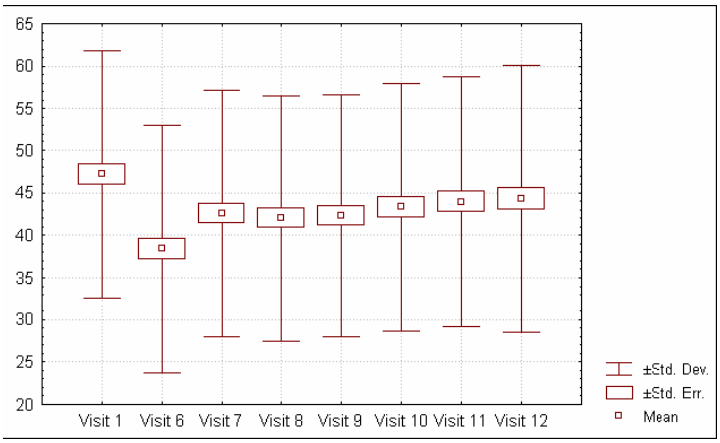
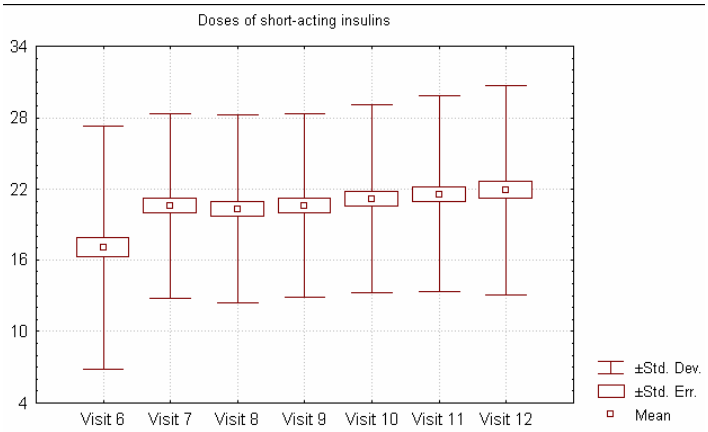


Fig. 2: Change of the rate of noctural hypoglycemia during the study treatment

Efficacy results:	International units of Insulin  Fig. 3: Change in the daily insulin glargine dose during the study treatment International Units of Insulin  Fig 4. Change in dose of insulin glulisine during the study treatment

<table>
<tr><td>Safety results:</td><td>Only 13 patients during the study experienced adverse events (9.2%).
<table>
<tr><th>Adverse events (AE)</th><th>Relationship to the study medication</th></tr>
<tr><td>Acute respiratory disease-7 cases</td><td>non related (registered during the cold time of the year-typical for climate zone in this period)</td></tr>
<tr><td>Food poisoning-1</td><td>non related</td></tr>
<tr><td>Rubella</td><td>non related</td></tr>
<tr><td>Acute nephritis</td><td>non related</td></tr>
<tr><td>Acute bronchitis</td><td>non related</td></tr>
<tr><td>Acute cholecystitis</td><td>non related</td></tr>
<tr><td>Pulmonary tuberculosis</td><td>non related</td></tr>
</table></td></tr>
<tr><td>Date of report:</td><td>14 June 2005</td></tr>
</table>